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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/708,204	02/16/2004	**Itzhak Bentwich**	050992.0201.03USCP	2203

37808 7590 03/31/2008

ROSETTA-GENOMICS
c/o PSWS
700 W. 47TH STREET
SUITE 1000
KANSAS CITY, MO 64112

EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/708,204	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/4/08 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 2/4/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/4/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 2/4/08, claims 31, 32, and 39-42 are pending and under examination.

Sequences—Notice to Comply

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The drawings and specification do not comply with 37 CFR §1.821(d), which states:

> 37 CFR § 1.821 Nucleotide and/or amino acid sequence disclosures in patent applications –
>
> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In the instant case, the sequences set forth in paragraphs 283-286, and 307 of the specification are not identified with SEQ ID NO: identifiers as required by the Rules. Applicant is requested to amend the specification to assign each sequence a corresponding SEQ ID NO: and to include such sequences in the sequence listing. Applicant is advised the cited paragraphs are by way of illustration only and not intended to be an all inclusive listing of sequences set forth in the specification. Applicant is specifically directed to review the entire disclosure, including the entire specification and each drawing, to ensure compliance with the Sequence Rules.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Similarly, acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a)-(d), 119(e), and 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of prior-filed Application Nos. 60/468,251, 10/649,653, 10/651,227, 10/707,147 11/24/2003, 10/604,985, 10/604,926, 10/604,727, 10/604,726, 10/707,975, 10/707,980, and PCT/IL03/00998 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for the instant claims drawn to SEQ ID NO:6527 and 15. That is, written description support for SEQ ID NO:6527 and 15 is not readily found in any of the prior filed applications to which priority is now claimed.

Therefore, for purposes of this examination the earliest effective filing date of the instant claims is considered to be that of the instant application: 2/16/2004.

Claim Objections

Claims 39 and 40 are objected to because the claims expressly claim vectors comprising an RNA. Ordinarily, the term "vector" is construed in the art to be a recombinant vehicle consisting entirely of DNA, not RNA. The specification teaches nothing different. Thus, it is unclear how a vector may comprise either SEQ ID NO:6527 or 15, which are each RNA. A vector may reasonably comprise a sequence encoding said sequences.

Claim Rejections - 35 USC § 101 and 112, First Paragraph

Claims 31, 32, and 39-42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a substantial or credible asserted utility.

Response to Arguments

To be clear, while the previous rejection under this section, mailed 9/4/07, rejected the claims as not being supported by a substantial asserted utility, the rejection herein and going forward is based primarily on a lack of credible asserted utility. Thus, the Examiner agrees with Applicant that an isolated nucleic acid capable of inhibiting the expression of a specific gene such as choline acetyltransferase (ChAT) or SERPINA3 satisfies the specific and substantial criteria of the utility requirement. See MPEP 2107-2107.03. Here, Applicant asserts the claimed nucleic acids may be used to inhibit the expression of at least two different genes. Nevertheless, the assertion is not credible for the reasons given below. As a result, the substantial and credible utility of sequences complementary to these miRNAs remains questionable. The claims are drawn to both the miRNAs and their complements.

Applicant's arguments and the Declaration under 37 CFR 1.132 filed 2/4/08 have been fully considered but are not persuasive for the reasons enumerated below.

In previous Office Actions, mailed 1/31/07 and 9/4/07, the Office has presented evidence suggesting there would have been reason at the time of filing to doubt the objective truth of the asserted utility. Further evidence is presented herein.

In brief, the instant application claims bioinformatically predicted preprocessed and mature miRNA sequences corresponding to SEQ ID NO:6527 and 15, respectively. SEQ ID NO:15 is said by Applicant to bind and inhibit ChAT and SERPINA3 mRNA targets, based on bioinformatically predicted alignments, according to established rules governing miRNA target binding. Applicant asserts one of skill would more likely than not conclude the claimed nucleic acids may be used to modulate the expression of SERPINA3. Specific and substantial utility is thereby asserted based on bioinformatic data. The asserted utility has not been experimentally verified. Indeed, there is no experimental evidence of even a single biological function. Function is asserted solely on the basis of a computer program designed to predict miRNA-like hairpin sequences and mature miRNAs derived therefrom by Dicer-catalyzed processing, which information is mined from raw genomic sequences.

At issue, then, is whether one of skill would more likely than not believe the nucleic acids predicted by Applicant's algorithm, such as the sequences now claimed, would have the specific and substantial utility predicted by the program.

1. The Declaration under 37 CFR 1.132 filed 2/4/08 has been fully considered, but is insufficient to overcome the rejection of claims in view of the totality of the evidence in the pre- and post-filing art. Though made by a proclaimed expert in the art, and containing sound scientific reasoning, the Declaration represents nothing more than an opinion. While the declaration quantifies the effectiveness

of other miRNA prediction algorithms, the declaration does not directly quantify the accuracy and/or false positive/false negative rate of the Inventor's algorithm, the program in question. Instead, the Declaration attempts to show the veracity of the instant prediction software by comparison to related prediction programs. Though unclear from the declaration, the assertion appears to be the instant algorithm is at least as effective as prior art algorithms. However, post-filing art (cited below) indicates it is difficult if not impossible to compare different algorithms without comparing their output using a common dataset, which does not appear to have been done here. The Declaration provides no experimental evidence validating either the predictive quality of the instant algorithm or the utility of the instantly claimed sequences. Such evidence if collected in a statistically relevant manner would be indicative of the accuracy of the algorithm.

2. The Declaration similarly fails to address the utility of isolated nucleic acids complementary to either SEQ ID NO:6527 or 15. These sequences would clearly not be complementary to the target mRNA. The only perceived utility would be to either inhibit or detect the bioinformatically predicted miRNAs themselves. However, there is absolutely no evidence, beyond the algorithm, that the claimed miRNAs are biologically active in any manner, or even expressed by any cell. Thus, the complements to SEQ ID NO:6527 and 15 lack both substantial and credible utility since there is no evidence the targets of these complements have any utility or that any information of immediate, real-world value could be obtained from the use of sequences complementary to SEQ ID NO:6527 and 15.

3. The question remains whether the bioinformatically predicted miRNAs now claimed would, more likely than not, have the utility asserted. The answer lies in the predictive quality of the program used to identify the miRNAs and their target sites. A quantifiable value is not readily apparent to the Examiner from the facts of record. Indeed, the Examiner is unable to find any disclosure by the inventor either in the instant application or in the pre- or post-filing art clearly articulating the sensitivity or false positive rate of the instant algorithm. A simple statement supported by actual experimental evidence, showing the algorithm correctly predicts an miRNA and its activity more than half of the time and has an acceptable false positive rate would be sufficient to overcome the instant rejection.
4. Currently, however, neither the Declaration nor the specification addresses this question directly or completely. In somewhat general terms the specification states at paragraph 275 that "assuming 80% accuracy of the HAIRPIN DETECTOR 114 and 80% accuracy of the DICER-CUT LOCATION DETECTOR 116 and 80% accuracy of the lab validation, this would result in 50% overall accuracy of the GAM oligonucleotide validated in the lab." Thus, it would seem the instant algorithm is correct about 50% of the time.
5. Further, it would appear from the teachings in the specification that multiple determinants govern the selection process.
6. Comparative algorithms used in the art are said to have false positive rates of between 22% and 39%. See Bentwich et al. (2005) *FEBS Lett.* 579:5904-5910,

page 5907; and the Declaration, Point 4. See also Martin et al. (2007) *J. Biosci.* 32:1049-1052 at page 1049, 4th full paragraph.

7. Martin et al. (2007) *J. Biosci.* 32:1049-1052, reviewing the state of the art of miRNA prediction programs, state mammalian miRNA targets are considered difficult to predict because miRNA targets display only partial complementarity to the mature miRNA sequence (pg. 1049). Martin et al. further state that "Given the high level of both false-positives and false-negatives resulting from the application of current miRNA target prediction programs, it is clear that experimental testing of predicted miRNA targets is critically important in order to validate/confirm any putative miRNA-target gene combination" (pg. 1050, 4th complete paragraph). Martin et al. further teach that miRNA prediction programs rely on sequence, structure, and evolutionary conservation information to predict genes likely to be targeted by miRNAs, but that the requirement for conserved sites means that non-conserved sites, which may represent real targets, are completely missed.
8. The post-filing art suggests that it is difficult to estimate the true false positive/negative rates of miRNA prediction programs because few validated miRNA targets are known. See Maziere et al. (2007) *Drug Discovery Today* 12:452-458, page 457. Maziere et al. in their article entitled "Prediction of miRNA Targets," further state that comparison of miRNA prediction efficiencies among different programs is not currently possible because many of the programs are not available for download and use on a common dataset; thus, Maziere et al.

cast doubt on the reliability of the statements made in the Declaration, comparing similar programs to that used by the Inventor. Again, no evidence has been presented by Declarant directly comparing the output of the instant algorithm with the other cited programs when presented with a common dataset. Thus, there is no objective evidence to corroborate Declarant's opinion.

9. Smalheiser et al. (2006) *Methods Mol. Biol.* 342:115-127 in an article entitled "Complications in miRNA Target Prediction" state that complementarity between miRNAs and their targets is not the only factor that may govern which miRNA-mRNA target interactions are effective in vivo. One must consider the potential importance of mRNA target secondary structure, as well as the strong possibility that RNA-binding proteins may participate in miRNA recognition. Furthermore, both miRNA and mRNA need to be coexpressed in proper amounts within the cell for effective interaction to occur, and A-to-I editing of RNA might abrogate potential mRNA targets from being effectively silenced by the RNA-induced silencing complex (page 124). Smalheiser et al. further teach that not all mammalian miRNAs interact with their targets via "short seeds," complementary regions of 6-8 nucleotides, but, instead, may interact via "long" seeds and perfect matches (page 115-6), and because new miRNAs are constantly being discovered this list of binding determinants may not be complete.

10. A search of putative target sites of the claimed miRNA, SEQ ID NO:15, using the miRanda program available at www.microrna.org, finds hundreds of putative target sites in hundreds of genes.

11. Thus, multiple factors are involved in miRNA-target binding and recognition.
12. Thus, in view of the totality of the evidence, one of skill would have reason to doubt the objective truth of the asserted utility. While the instant algorithm provides a list of putative miRNAs and corresponding target sites, there is reason to question whether the bioinformatic algorithm used to produce this list correctly identifies an miRNA and its function (i.e., at least one biological function) with minimally acceptable false positive and false negative rates such that one of skill would believe the miRNA would, more likely than not, inhibit the gene predicted by the software. Without experimental validation or any verifiable evidence of the accuracy and error rates of the instant program, and in view of the state of the art at the time of invention, one of skill would reasonably question the certainty of the prediction at the time of filing.
13. The skilled artisan would be led to believe only that the instantly claimed nucleic acids require further research to verify the asserted utility.

***

Claims 14, 26, 30, and 32 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claims 31-36, 41, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Random Primer 24, sold by New England Biolabs (see page 121 of the 1998/99

New England Biolabs Catalog) (New England Biolabs 1998/99 Catalog, cover page, page 121 and 284) is withdrawn in view of Applicant's amendments to the claims.

***

The rejection of Claims 31-36, 41, and 42 under 35 U.S.C. 102(b) as being anticipated by Fodor et al. (US Patent 6,582,908, published as US 2001/0053519 A1 on Dec. 20, 2001) is withdrawn in view of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 102—new

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 40 and 42 are rejected under 35 U.S.C. 102(e) as being anticipated by Croce et al. (US20060105360A1).

Claim interpretation:

The claims use open "comprising" language. Accordingly, the claimed vectors and probes may comprise the isolated nucleic acid as well as additional sequences. A "probe" is reasonably interpreted to embrace DNA and RNA sequences. Moreover, a "complement of" either SEQ ID NO:6527 or 15 is reasonably interpreted to include both DNA and RNA sequences

complementary to either sequence. Similarly, claims 39 and 40 each recite vectors comprising any of the isolated nucleic acids claimed in claims 31 or 32; the claims are definite inasmuch as vectors normally consist of DNA, not RNA, and because claims 31 and 32 embrace DNA complements. Nevertheless, despite the language, claims 39 and 40 are herein construed to embrace vectors encoding SEQ ID NO:6527 or 15 or complements thereof. See Claim Objection above.

The rejection:

Citing from US Provisional Application 60/543119, Croce et al. taught several human miR Gene Product Sequences, culled from miR Registry, published papers, and GenBank. The precursor sequences were predicted by use of an RNA folding program (page 35).

In particular, Croce et al. taught a 69-nucleotide sequence (shown below) said to comprise the precursor microRNA hsa-mir-151 (Table 1, page 45).

The hsa-mir-151-precursor set forth in Croce et al. has the following sequence. The underlined sequence is said to represent the processed miR transcript (page 51).

CCTGCCCTCGAGGAGCTCACAGTCTAGTATGTCTCATCCCCT

ACTAGACTGAAGCTCCTTGAGGACAGG

As shown by the alignments below, the 69-nucleotide sequence comprises instant SEQ ID NO:15 and nucleotides 37-105 of instant SEQ ID NO:6527. Croce et al. further taught that the expression and/or presence of particular miRNAs may be determined by Northern blotting using suitable probes produced from any of the nucleic acids listed in Table 1 (page 16). It is further taught the miR gene products may be expressed recombinantly from plasmids or viral vectors (pages 22-25).

For convenience, instant SEQ ID NO: 15 and 6527 are reproduced herein:

SEQ ID NO: 15 cuagacugaa gcuccuugag ga

SEQ ID NO:6527 gcuagucacu ggggcaaaga ugacuaaaac acuuuuccug cccucgagga gcucacaguc 60

uaguaugucu caucccccuac uagacugaag cuccuugagg acagggaugg ucauacucac 120

cucgguguug c

```
RESULT 5
US-11-194-055-174
; Sequence 174, Application US/11194055
; Publication No. US20060105360A1
; GENERAL INFORMATION:
;  APPLICANT: Croce, Carlo M.
;  APPLICANT:  Liu, Chang-Gong
;  APPLICANT:  Calin, George, A.
;  APPLICANT:  Cinzia, Sevignani
;  TITLE OF INVENTION: DIAGNOSIS AND TREATMENT OF CANCERS WITH
;  TITLE OF INVENTION:  MicroRNA LOCATED IN OR NEAR CANCER-ASSOCIATED CHROMOSOMAL
;  TITLE OF INVENTION:  FEATURES
;  FILE REFERENCE: 3589.1018-008
;  CURRENT APPLICATION NUMBER: US/11/194,055
;  CURRENT FILING DATE:  2005-07-29
;  PRIOR APPLICATION NUMBER: PCT/US2005/004865
;  PRIOR FILING DATE: 2005-02-09
;  PRIOR APPLICATION NUMBER: 60/543,119
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/542,929
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/542,963
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/542,940
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/580,959
;  PRIOR FILING DATE: 2004-06-18
;  PRIOR APPLICATION NUMBER: 60/580,797
;  PRIOR FILING DATE: 2004-06-18
;  NUMBER OF SEQ ID NOS: 663
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 174
;   LENGTH: 69
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-11-194-055-174

  Query Match             52.7%;  Score 69;  DB 21;  Length 69;
  Score over Length       100.0%;
  Best Local Similarity   76.8%;  Pred. No. 6.4e-15;
  Matches   53;  Conservative   16;  Mismatches    0;  Indels    0;  Gaps    0;

Qy         37 CCUGCCCUCGAGGAGCUCACAGUCUAGUAUGUCUCAUCCCCUACUAGACUGAAGCUCCUU 96
              ||:||||:||||||||:|||||:|:||:|:|:|:||:||||:||:||||:|||||:||::
Db          1 CCTGCCCTCGAGGAGCTCACAGTCTAGTATGTCTCATCCCCTACTAGACTGAAGCTCCTT 60

Qy         97 GAGGACAGG 105
              |||||||||
Db         61 GAGGACAGG 69

RESULT 5
US-11-194-055-174
; Sequence 174, Application US/11194055
; Publication No. US20060105360A1
; GENERAL INFORMATION:
;  APPLICANT: Croce, Carlo M.
;  APPLICANT:  Liu, Chang-Gong
;  APPLICANT:  Calin, George, A.
;  APPLICANT:  Cinzia, Sevignani
;  TITLE OF INVENTION: DIAGNOSIS AND TREATMENT OF CANCERS WITH
;  TITLE OF INVENTION:  MicroRNA LOCATED IN OR NEAR CANCER-ASSOCIATED CHROMOSOMAL
;  TITLE OF INVENTION:  FEATURES
;  FILE REFERENCE: 3589.1018-008
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;  CURRENT APPLICATION NUMBER: US/11/194,055
;  CURRENT FILING DATE:  2005-07-29
;  PRIOR APPLICATION NUMBER: PCT/US2005/004865
;  PRIOR FILING DATE: 2005-02-09
;  PRIOR APPLICATION NUMBER: 60/543,119
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/542,929
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/542,963
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/542,940
;  PRIOR FILING DATE: 2004-02-09
;  PRIOR APPLICATION NUMBER: 60/580,959
;  PRIOR FILING DATE: 2004-06-18
;  PRIOR APPLICATION NUMBER: 60/580,797
;  PRIOR FILING DATE: 2004-06-18
;  NUMBER OF SEQ ID NOS: 663
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 174
;   LENGTH: 69
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-11-194-055-174

  Query Match             100.0%;  Score 22;  DB 21;  Length 69;
  Best Local Similarity   77.3%;  Pred. No. 2;
  Matches   17;  Conservative    5;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CUAGACUGAAGCUCCUUGAGGA 22
              |:||||:|||||:||::|||||
Db         44 CTAGACTGAAGCTCCTTGAGGA 65
```

Therefore, Croce et al. anticipate the instant claims.

In order to constitute anticipatory prior art, a reference must identically disclose the claimed compound, but no utility need be disclosed by the reference. *In re Schoenwald,* 964 F.2d 1122, 22 USPQ2d 1671 (Fed. Cir. 1992) (The application claimed compounds used in ophthalmic compositions to treat dry eye syndrome. The examiner found a printed publication which disclosed the claimed compound but did not disclose a use for the compound. The court found that the claim was anticipated since the compound and a process of making it was taught by the reference. The court explained that "no utility need be disclosed for a reference to be anticipatory of a claim to an old compound." 964 F.2d at 1124, 22 USPQ2d at 1673. It is enough that the claimed compound is taught by the reference.). >See also *Impax Labs. Inc. v. Aventis Pharm. Inc.,* 468 F.3d 1366, 1383, 8 USPQ2d 1001, 1013 (Fed. Cir. 2006) ("[P]roof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation."). See MPEP § 2122.

***

Claim 39 is rejected under 35 U.S.C. 102(e) as being anticipated by Venter et al. (US Patent 6,812,339).

As shown by the alignment below, Venter et al. taught a nucleic acid sequence comprising instant SEQ ID NO:6527. Venter et al. taught recombinant vectors comprising said said sequence (see disclosure beginning at column 19, for example).

```
RESULT 1
US-09-949-016-13165
; Sequence 13165, Application US/09949016
```

```
; Patent No. 6812339
; GENERAL INFORMATION:
;  APPLICANT: VENTER, J. Craig et al.
;  TITLE OF INVENTION: POLYMORPHISMS IN KNOWN GENES ASSOCIATED
;  TITLE OF INVENTION:  WITH HUMAN DISEASE, METHODS OF DETECTION AND USES THEREOF
;  FILE REFERENCE: CL001307
;  CURRENT APPLICATION NUMBER: US/09/949,016
;  CURRENT FILING DATE:  2000-04-14
;  PRIOR APPLICATION NUMBER: 60/241,755
;  PRIOR FILING DATE: 2000-10-20
;  PRIOR APPLICATION NUMBER: 60/237,768
;  PRIOR FILING DATE: 2000-10-03
;  PRIOR APPLICATION NUMBER: 60/231,498
;  PRIOR FILING DATE: 2000-09-08
;  NUMBER OF SEQ ID NOS: 207012
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 13165
;   LENGTH: 346112
;   TYPE: DNA
;   ORGANISM: Human
;   FEATURE:
;   NAME/KEY: misc_feature
;   LOCATION: (1)...(346112)
;   OTHER INFORMATION: n = A,T,C or G
US-09-949-016-13165

  Query Match             100.0%;  Score 131;  DB 3;  Length 346112;
  Best Local Similarity   74.8%;  Pred. No. 6.3e-38;
  Matches   98;  Conservative   33;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GCUAGUCACUGGGGCAAAGAUGACUAAAACACUUUUCCUGCCCUCGAGGAGCUCACAGUC 60
              ||:||:|||:||||||||||:|||:|||||||:::::||:||||:||||||||:|||||:|
Db     270570 GCTAGTCACTGGGGCAAAGATGACTAAAACACTTTTCCTGCCCTCGAGGAGCTCACAGTC 270629

Qy         61 UAGUAUGUCUCAUCCCCUACUAGACUGAAGCUCCUUGAGGACAGGGAUGGUCAUACUCAC 120
              :||:|:|:|:||:||||:||:||||:|||||:||::||||||||||||:||:||:|||
Db     270630 TAGTATGTCTCATCCCCTACTAGACTGAAGCTCCTTGAGGACAGGGATGGTCATACTCAC 270689

Qy        121 CUCGGUGUUGC 131
              |:|||:|::||
Db     270690 CTCGGTGTTGC 270700
```

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Claim 40 is rejected under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (1997) GenBank Acc. No. AQ420078, first seen at NCBI on Mar 23 1999 12:30 AM.

As shown by the alignment below, Zhao et al. taught an isolated 684-nucleotide DNA sequence and BAC clone thereof comprising a sequence complementary to instant SEQ ID NO: 15

```
RESULT 1
AQ420078/c
LOCUS       AQ420078               684 bp    DNA     linear   GSS 23-MAR-1999
DEFINITION  RPCI-11-188K5.TV RPCI-11 Homo sapiens genomic clone RPCI-11-188K5,
            genomic survey sequence.
ACCESSION   AQ420078
VERSION     AQ420078.1  GI:4477802
KEYWORDS    GSS.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 684)
  AUTHORS   Zhao,S., Adams,M.D., Nierman,W., Malek,J., de Jong,P. and
```

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            Venter,J.C.
  TITLE     Use of BAC End Sequences from Library RPCI-11 for Sequence-Ready
            Map Building
  JOURNAL   Unpublished (1997)
COMMENT     Other_GSSs: RPCI-11-188K5.TJ
            Contact: Shaying Zhao, William Nierman, Mark Adams
            Department of Eukaryotic Genomics
            The Institute for Genomic Research
            9712 Medical Center Dr., Rockville, MD 20850
            Tel: 301 838 0200
            Fax: 301 838 0208
            Email: hbe@tigr.org
            Clones are derived from the human BAC library RPCI-11. For BAC
            library availability, please contact Pieter de Jong
            (pieter@dejong.med.buffalo.edu). Clones may be purchased from
            BACPAC Resources (http://bacpac.med.buffalo.edu/ordering) or from
            Research Genet cs (info@resgen.com). BAC end search page:
            http://www.tigr.org/tdb/humgen/bac_end_search/bac_end_search.html.
            Seq primer: T7
            Class: BAC ends.
FEATURES             Location/Qualifiers
     source          1. .684
                     /organism="Homo sapiens"
                     /mol_type="genomic DNA"
                     /db_xref="GDB:7572052"
                     /db_xref="taxon:9606"
                     /clone="RPCI-11-188K5"
                     /sex="Male"
                     /cell_type="Lymphocytes"
                     /clone_lib="RPCI-11"
                     /note="Vector: pBACe3.6; Site_1: EcoRI; Site_2: EcoRI;
                     RPCI11 Human Male BAC Library"
ORIGIN

  Query Match             95.0%;  Score 124.4;  DB 15;  Length 684;
  Best Local Similarity   73.8%;  Pred. No. 3e-30;
  Matches   93;  Conservative   32;  Mismatches    1;  Indels    0;  Gaps    0;

Qy          6 UCACUGGGGCAAAGAUGACUAAAACACUUUUCCUGCCCUCGAGGAGCUCACAGUCUAGUA 65
              :|||:||||||||||:|||:|||||||::::| :||||:||||||||:|||||:|:||:|
Db        684 TCACTGGGGCAAAGATGACTAAAACACTTTTCATGCCCTCGAGGAGCTCACAGTCTAGTA 625

Qy         66 UGUCUCAUCCCCUACUAGACUGAAGCUCCUUGAGGACAGGGAUGGUCAUACUCACCUCGG 125
              :|:|:||:||||:||:||||:|||||:||::||||||||||:||:||:||:||||:|||
Db        624 TGTCTCATCCCCTACTAGACTGAAGCTCCTTGAGGACAGGGATGGTCATACTCACCTCGG 565

Qy        126 UGUUGC 131
              :|::||
Db        564 TGTTGC 559
```

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Venter et al. (US Patent 6,812,339), as applied to claim 39 above, and further in view of Buck et al. (Biotechniques (1999) 27(3): 526-538).

Venter et al. is relied on for the reasons given above and those that follow. Venter et al. taught the use of probes and primers to detect and amplify the disclosed nucleic acids. It is said a probe or primer typically comprises a substantially purified oligonucleotide or oligonucleotide pair. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 20, 25, 40, 50 or more consecutive nucleotides, and that the primer and probe sequences can readily be determined using the sequences disclosed.

While Venter et al. do not expressly teach probes and primers comprising instant SEQ ID NO:6527 or its complement, in view of the disclosure of Buck et al., it would have been obvious to one of skill in the art at the time of invention that almost any complementary seqence of essentially any length suitable for detection of a nucleic acid could have been used to detect the sequence disclosed therein as SEQ ID NO:13165.

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby

testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

Because primers and probes bind to their targets according to the same principles, it would be obvious to one of skill that each may be used according to the same purpose with the expectation each would bind the complementary target, whether via Northern blotting or in solution. In fact, one of skill would have even greater expectation of success given that probes need simply bind via Watson-Crick base-pairing and do not need to be extended as during PCR.

Therefore it would have been prima facie obvious at the time of invention to make and use nucleic acid probes against essentially any region of the Venter et al. sequences SEQ ID NO:13165 with anticipated success of detecting and or amplifying the corresponding sequence in said SEQ ID NO:13165.

Finally, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

Prior art made of record but not currently relied on

Lagos-Quintana et al. (2002) *Curr. Biol.* 12:735-739 taught a 22-nucleotide mouse miRNA, disclosed therein as miR-151, closely related and structurally similar to instant SEQ ID NO:15. See alignment below.

```
RESULT 16
MMU459763
LOCUS       MMU459763                22 bp    mRNA    linear   ROD 05-JUL-2002
DEFINITION  Mus musculus microRNA miR-151.
ACCESSION   AJ459763
VERSION     AJ459763.1  GI:20799081
KEYWORDS    microRNA miR-151; miR-151 gene; miRNA.
SOURCE      Mus musculus (house mouse)
  ORGANISM  Mus musculus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Muridae; Murinae; Mus.
REFERENCE   1
  AUTHORS   Lagos-Quintana,M., Rauhut,R., Yalcin,A., Meyer,J., Lendeckel,W. and
            Tuschl,T.
  TITLE     Identification of tissue-specific microRNAs from mouse
  JOURNAL   Curr. Biol. 12 (9), 735-739 (2002)
   PUBMED   12007417
REFERENCE   2  (bases 1 to 22)
  AUTHORS   Tuschl,T.
  TITLE     Direct Submission
  JOURNAL   Submitted (06-MAY-2002) Dep. of Cellular Biochemistry, Max Planck
            Institute for Biophysical Chemistry, Am Fassberg 11, Goettingen
            37077, Germany
COMMENT     related sequence: TI88456669 (Trace Archive).
FEATURES             Location/Qualifiers
     source          1. .22
                     /organism="Mus musculus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10090"
     gene            1. .22
                     /gene="miR-151"
     misc_RNA        1. .22
                     /gene="miR-151"
                     /product="microRNA miR-151"
                     /note="transcribed as larger precursor, predicted to form
                     hairpin"
ORIGIN

  Query Match           14.8%;  Score 19.4;  DB 6;  Length 22;
  Score over Length     88.2%;
  Best Local Similarity 71.4%;  Pred. No. 9.8e+04;
```

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  Matches   15;  Conservative    5;  Mismatches    1;  Indels    0;  Gaps    0;

Qy         80 CUAGACUGAAGCUCCUUGAGG 100
              |:||||:|| ||:||::||||
Db          1 CTAGACTGAGGCTCCTTGAGG 21
```

***

Kim et al. (2004) *PNAS* 101:360365 and Table 2, published online 12/22/03, taught the sequence of rat mir-151, which sequence is nearly identical to the complement of instant SEQ ID NO:15. See Table 2 (Supplementary material) therein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Examiner, AU1635
March 20, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635